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PMID: 2154604 [PubMed - indexed for MEDLINE]

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Cell-mediated immunological responses in cervical and vaginal cancer patients immunized with a lipidated epitope of human papillomavirus type 16 E7.

Steller MA, Gurski KJ, Murakami M, Daniel RW, Shah KV, Celis E, Sette A, Trimble EL, Park RC, Marincola FM.

Section of Gynecologic Oncology, Surgery Branch, Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland 20892, USA. msteller@wihri.org

Human papillomavirus (HPV) infection has been causally associated with cervical cancer. We tested the effectiveness of an HLA-A*0201-restricted, HPV-16 E7 lipopeptide vaccine in eliciting cellular immune responses in vivo in women with refractory cervical cancer. In a nonrandomized Phase I clinical trial, 12 women expressing the HLA-A2 allele with refractory cervical or vaginal cancer were vaccinated with four E786-93 lipopeptide inoculations at 3-week intervals. HLA-A2 subtyping was also performed, and HPV typing was assessed on tumor specimens. Induction of epitope-specific CD8+ T-lymphocyte (CTL) responses was analyzed using peripheral blood leukapheresis specimens obtained before and after vaccination. CTL specificity was measured by IFN-gamma release assay using HLA-A*0201 matched target cells. Clinical responses were assessed by physical examination and radiographic images. All HLA-A*0201 patients were able to mount a cellular immune response to a control peptide. E786-93-specific CTLs were elicited in 4 of 10 evaluable HLA-A*0201 subjects before vaccination, 5 of 7 evaluable HLA-A*0201 patients after two vaccinations, and 2 of 3 evaluable HLA-A*0201 cultures after all four inoculations. Two of three evaluable patients' CTLs converted from unreactive to reactive after administration of all four inoculations. There were no clinical responses or treatment toxicities. The ability to generate specific cellular immune responses is retained in patients with advanced cervical cancer. Vaccination with a lipidated HPV peptide epitope appears capable of safely augmenting CTL reactivity. Although enhancements of cellular immune responses are needed to achieve therapeutic utility in advanced cervical cancer, this approach might prove useful in treating preinvasive disease.

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1: J Immunother 1998 Nov;21(6):399-408 Related Articles, Books, LinkOut

Peptide vaccination with an anchor-replaced CTL epitope protects against human papillomavirus type 16-induced tumors expressing the wild-type epitope.

Vierboom MP, Feltkamp MC, Neisig A, Drijfhout JW, ter Schegget J, Neefjes JJ, Melief CJ, Kast WM.

Department of Immunohematology & Blood Bank, University Hospital Leiden, The Netherlands.

Anchor residues in cytotoxic T-lymphocyte (CTL) epitope-bearing peptides are buried deep in the major histocompatibility complex (MHC) class I antigen-presenting groove and are essential for binding to MHC class I molecules. We investigated whether anchor residue replacement affects the ability of a CTL epitope to be bound and transported by MHC class I molecules and transporter associated with antigen (TAP), respectively, and affects its functionality in vivo. Therefore, both anchor residues, at positions 5 and 9, of the H-2Db-restricted CTL epitope HPV16 E7 49-57 RAHYNIVTF were systematically exchanged for one of the 19 other naturally occurring amino acid (AA). Only replacement at anchor position 9 with residues V, I, L, or M, which are documented Db motif-anchor residues at that position, allowed binding to the MHC class I H-2Db molecule as well as transport by TAP with the same efficiency as the wild-type epitope. In B6 mice (H-2b), these anchor-modified peptide epitopes efficiently induced CTL that specifically recognized the wild-type epitope. Conversely, wild-type epitope-induced CTL recognized the V9-, I9-, L9-, and M9-replaced epitopes, respectively. In terms of tumor protection against a challenge with HPV16-transformed cells, the V9-replaced epitope was as efficient as the wild-type epitope E7 49-57. Taken together, our data demonstrate that specific CTL epitope anchor replacements are allowed with respect to MHC class I binding and TAP transport, as well as with respect to antigenicity and immunogenicity in vivo. The results presented are relevant to CTL epitope-based peptide vaccine development.

PMID: 9807734 [PubMed - indexed for MEDLINE]